REMARKS

Claims 5-7 and 13-15 are all the claims pending in the application; claims 5-7 are rejected; claims 13-15 have been withdrawn from consideration.

Support for new claims 38-40 may be found in the specification at page 10, lines 9-20.

Upon allowance of claim 5, Applicants respectfully request rejoinder of claims 39-40 as they recite each and every limitation of product claim 5.

No new matter has been added. Entry of the Amendment is respectfully requested.

I. Formal Matters

A. Applicants note that an Information Disclosure Statement was filed in this application on February 20, 2003, along with a document list. While the Examiner returned a signed and initialed copy of the list to Applicants on May 10, 2004, the two cited U.S. patents were not initialed. Applicants enclose a copy of the document list herewith and respectfully request the Examiner to return a signed and initialed copy of the list, indicating consideration of the two U.S. patents.

B. Applicants note that formal drawing were filed in this application on December 10, 2001. Applicants respectfully request that the Examiner acknowledge acceptance of the formal drawings.

II. Claim Rejections Under 35 U.S.C. §103

At page 2 of the Office Action, claims 5-7 remain rejected under 35 U.S.C. §103(a) for the reasons set forth in the Office Action dated June 17, 2005, pages 5-8.

In the Office Action dated June 17, 2005, the Examiner rejected claims 5-7 under 35 U.S.C. §103(a) as being unpatentable over Purnelle et al. (GenBank accession number P25371) or Kirby et al. (GenBank accession number Q94960) and further in view of Harlow et al. (Antibodies, A Laboratory Manual, Cold Spring Harbor Press, 1988, p. 142).

Briefly, the Examiner contends that Purnelle et al. and Kirby each teach polypeptides that contain regions of five or more consecutive amino acids that either share identity with or are conservative substitutions for amino acids regions found in SEQ ID NO:1, and that a subset of these regions of amino acid homology would be expected to comprise antibody epitopes that are

shared with the polypeptide of SEQ ID NO:1. The Examiner believes that it would have been *prima facie* obvious to the skilled artisan to produce monoclonal antibodies (mAbs) to either the Purnelle or Kirby polypeptides because the U.S. PTO BPAI has taken the position that once a polypeptide is known, monoclonal antibodies against the polypeptide are *prima facie* obvious.

Applicants note that in order for the Examiner to maintain a rejection under 35 U.S.C. §103, the Examiner must show (1) that the cited references teach each and every element of the claim, (2) that there is a suggestion or motivation in the cited references or the general knowledge of the art to modify the references to make the claimed invention, and (3) that there is a reasonable expectation of success that the modification will yield the claimed subject matter. *In re Vaeck*, 947 F.2d 488, 20 USPQ2d 1438 (Fed. Cir. 1991). See also MPEP §2142.

A rejection under 35 U.S.C. §103 may be traversed by arguing that the Examiner has not established one or more of the elements of a *prima facie* showing of obviousness.

For the following reasons, Applicants respectfully traverse the rejection as the Examiner has not established a *prima facie* showing of obviousness.

A. The cited references do not teach each and every limitation of the claims

The Examiner states that it would have been *prima facie* obvious to one of ordinary skill in the art at the time of the invention to have produced antibodies to either or both of the polypeptides of Purnelle and Kirby.

However, the Examiner has not provided any indication that the particular species of antibodies recited in the pending claims (those that bind the polypeptide of SEQ ID NO:1) would be included in the genus of antibodies that would result from the use of the Purnelle or Kirby polypeptides as an immunogen in the production of antibodies.

Applicants note that antibodies may be raised against either an entire polypeptide or against fragments of a polypeptide. If antibodies were to be raised against an entire polypeptide, a genus of antibodies with different binding specificities would be generated. As noted by Herbert et al.[1], cited by the Examiner in the Office Action, an epitope "may be formed from

[1] The Dictionary of Immunology, Forth Edition, Herbert et al. eds, Academic Press 1995.

residues on different regions of a protein antigen molecule which, in the native state, are closely apposed due to protein folding." Herbert et al. also notes that "the three-dimensional structure of the protein molecule may be essential for antibody binding." Thus, when an entire protein is used as an antigen, the antigenic determinants may be formed by residues located in different portions of the molecule.

The Examiner has presented no evidence that the polypeptide of Purnelle or Kirby has an antigenic determinant that is identical to an antigenic determinant of the polypeptide of claim 1. Indeed, as indicated by the Examiner, the Purnelle protein only shares 30.5% identity with the polypeptide of claim 1, and the Kirby protein only shares 32.1% identity with the polypeptide of claim 1. As noted by Herbert, the three-dimensional structure of the epitope is essential for antibody binding. The skilled artisan would not expect that two polypeptides having such a low degree of homology would form identical antigenic determinants in the native folding of the proteins as those found in the polypeptide of SEQ ID NO:1.

As such, the Examiner has presented no evidence to demonstrate or suggest that the genus of antibodies raised against either the Purnelle or Kirby polypeptide would also bind to the polypeptide of claim 1. Indeed, as stated in the enclosed Declaration Under 37 C.F.R. §1.132, in view of the low degree of homology, the skilled artisan would not expect antibodies raised against either the Purnelle or Kirby polypeptide to be cross-reactive with the polypeptide of SEQ ID NO:1.

As to antibodies raised against fragments of a polypeptide, the Examiner suggests that antibodies can be raised against peptides comprising five or more amino acids. The polypeptide of Purnelle contain 1049 amino acids, and the polypeptide of Kirby contains 634 amino acids (as shown on the enclosed NCBI printouts). Reducing either the Purnelle or the Kirby polypeptides to fragments of five amino acids would results in hundreds of different five residue fragments. As such, the genus of antibodies resulting from the use of fragments of the Purnelle and Kirby polypeptides would include hundreds of different antibodies.

The sequence alignment between the polypeptides of Purnelle and SEQ ID NO:1 recited in claim 1 provided by the Examiner only shows three regions of five or more identical amino

acids. The alignment between the polypeptides of Kirby and SEQ ID NO:1 only shows four regions of five or more identical amino acids.

Thus, the antibodies recited in claim 1 comprise a small number of species of the large genus of antibodies that might arise from the production of antibodies using fragments of the polypeptides of Purnelle and Kirby. There is nothing in the art cited by the Examiner that teaches employing selected fragments of the polypeptides of the cited art to produce antibodies that would bind to the polypeptide of SEQ ID NO:1. As noted in MPEP §2144.08: "a *prima facie* case of unpatentability requires that the teachings of the prior art suggest *the claimed compounds* to a person of ordinary skill in the art." *In re Deuel*, 51 F3d 1552, 1557, 34 USPQ2d 1210, 1214 (Fed. Cir. 1995).

As further noted in MPEP §2144.08:

> Some motivation to select the claimed species or subgenus must be taught by the prior art. See, e.g., Deuel, 51 F.3d at 1558-59, 34 USPQ2d at 1215 ("No particular one of these DNAs can be obvious unless there is something in the prior art to lead to the particular DNA and indicate that it should be prepared."); Baird, 16 F.3d at 382-83, 29 USPQ2d at 1552; Bell, 991 F.2d at 784, 26 USPQ2d at 1531 ("Absent anything in the cited prior art suggesting which of the 1036 possible sequences suggested by Rinderknecht corresponds to the IGF gene, the PTO has not met its burden of establishing that the prior art would have suggested the claimed sequences."). However, a genus may be so small that, when considered in light of the totality of the circumstances, it would anticipate the claimed species or subgenus. For example, it has been held that a prior art genus containing only 20 compounds and a limited number of variations in the generic chemical formula inherently anticipated a claimed species within the genus because "one skilled in [the] art would... envisage each member" of the genus.

As the art cited by the Examiner does not teach each and every limitation of the claims, the Examiner has not established a *prima facie* showing of obviousness.

B. No suggestion or motivation to make the claimed invention

There is no suggestion or motivation in the publications cited by the Examiner, or the general knowledge of the art, to make the claimed invention.

For the reasons discussed below, Applicants could only have produced antibodies that would bind to the polypeptide of SEQ ID NO:1 by using the specific regions of identity between the polypeptides of Purnelle and Kirby and that of SEQ ID NO:1. The skilled artisan would have needed to have identified the specific regions of identity, produced peptides comprising such regions, and raised antibodies against those regions. There is no suggestion or motivation in the art cited by the Examiner, or the general knowledge in the art, to make such selections and to produce such antibodies.

As there would have been no suggestion or motivation to make the claimed invention, the Examiner has again not established a *prima facie* showing of obviousness.

C. No reasonable expectation of success

The skilled artisan would not have had a reasonable expectation of success that antibodies raised against the polypeptides of Purnelle and Kirby would bind to the polypeptide of SEQ ID NO:1 (as recited in claim 1).

1. Antibodies would not cross-react with epitopes having non-identical amino acids

In the Office Action dated June 17, 2005, the Examiner states that Roitt et al. "specifically teach that when the determinants of antigen A are shared by another antigen, B, then antibodies that bind to those determinants in A will also react with B. However, it is important to note that Roitt et al. only teaches that antibodies may cross react with highly similar epitopes. As shown in Fig. 6.9 of the portion of the publication provided by the Examiner, antibody binding can be severely reduced by simply changing the position of an oxygen radical on a carbon ring (compare the radical of the sulphonate in the meta and para positions) or changing the size of one atom in the epitope (compare sulphonate and carboxylate where the radical is in the meta position). A slightly greater change, such as both altering the position of the radical and increasing or decreasing the size of an atom completely blocks antibody binding (compare sulphonate having the radical in the meta position with arsonate or carboxylate having the radical in the ortho position). Roitt et al. further states on page 6.5 of the publication, first full paragraph, that "[a]ntibodies are capable of expressing remarkable specificity, and are able to distinguish between small differences in the primary amino acid sequence of protein

antigens." As persistently noted by the U.S. PTO in rejections issued in applications with claims to antibody homologues, a change as small as one amino acid can completely block the ability of an antibody to bind an epitope. Indeed, the Examiner has stated that cross-reactive antibodies are those that bind specifically to other proteins that share the "same epitope" (page 5, line 16, of the Office Action dated June 17, 2005).

The Examiner also notes that Herbert et al. teaches antibodies "bind in a more or less exact three-dimensional fit with an epitope." While the Examiner suggests that Herbert et al. concludes "thus the exact constitution of the amino acids forming the epitope is not critical as long as their three-dimensional fit produces an epitope to which the antibody will bind" (page 5, lines 20-22, of the Office Action dated June 17, 2005), Applicants note that Herbert et al. neither makes such as statement or suggests such a conclusion. Instead, Herbert et al. goes on to state that the epitope "may be formed from residues on different regions of a protein antigen molecule which, in the native state, are closely apposed due to protein folding", and that "the three-dimensional structure of the protein molecule may be essential for antibody binding."

As such, the Examiner has not provided any support for her position (sentence bridging pages 5-6 of June 17, 2005 Office Action) that an antibody recognizing a protein comprising five or more amino acids would also recognize a protein having conservative amino acid substitutions. Indeed, as suggested by the documents cited by the Examiner, the skilled artisan would not expect an antibody to cross-react with an antigenic determinant differing in amino acid content from the antigen against which it was raised. This point is supported by the statements made in the Rule 132 Declaration filed herewith (page 3, lines 3-16).

2. Antibodies to native proteins would not be expected to cross-react

a. No evidence of shared 3-D structure

It is the Examiner's position that antibodies raised against the polypeptides of Purnelle and Kirby would likely include a subset of antibodies that would bind to the polypeptide of SEQ ID NO:1. Applicants respectfully note that antibodies raised against the polypeptides of Purnelle and Kirby would be raised against the native proteins, there being no suggestion in the art to raise antibodies to specific, isolated portions of these polypeptides. As such, the polypeptides of

Purnelle and Kirby will recognize antigenic determinants in the form of a three-dimensional confirmation. As noted by Herbert et al., epitopes may be formed from residues on different regions of the polypeptide. The Examiner has presented no evidence to suggest that the polypeptides of Purnelle and Kirby share an antigenic determinant (a three-dimensional conformation of residues forming an antibody binding site) in common with the polypeptide of SEQ ID NO:1. Indeed, given the low degree of identity between the polypeptides of Purnelle and Kirby, and the polypeptide of SEQ ID NO:1 (30.5% and 32.1%, respectively), the skilled artisan would not reasonably expect an antibody raised against the polypeptide of Purnelle or Kirby to bind to the polypeptide of SEQ ID NO:1 (see page 3, lines 3-16, of the Rule 132 Declaration).

b. Regions of identity not surface exposed or antigenic

Even if antibodies raised against the polypeptides of Purnelle and Kirby recognized discreet, contiguous portions of the polypeptides, the skilled artisan would again not have had a reasonable expectation of success in producing an antibody that would also bind to the polypeptide of SEQ ID NO:1.

As noted above, there are three regions of five or more identical amino acids shared by the polypeptide of Purnelle and that of SEQ ID NO:1, and four between the polypeptide of Kirby and that of SEQ ID NO:1. As discussed in the enclosed Rule 132 Declaration, there is no evidence that any of the seven regions are exposed on the surface of the Purnelle polypeptide, the Kirby polypeptide, or the polypeptide of SEQ ID NO:1. Furthermore, as discussed in the enclosed Rule 132 Declaration, there is no evidence that any of the seven regions are particularly antigenic. As such, even if antibodies were raised against the polypeptides of Purnelle and Kirby, the skilled artisan would not have expected an antibody to be produced that would recognize and bind one of the seven regions. In particular, because these seven regions have relatively low antigenicity, the skilled artisan would again not have had a reasonable expectation of success in raising antibodies that would recognize and bind the polypeptide of SEQ ID NO:1.

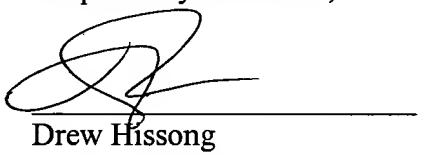
For each of the reasons discussed above, it is clear that the Examiner has not established a *prima facie* showing of obviousness. Accordingly, Applicants respectfully request reconsideration and withdrawal of this rejection.

III. Conclusion

In view of the above, reconsideration and allowance of this application are now believed to be in order, and such actions are hereby solicited. If any points remain in issue which the Examiner feels may be best resolved through a personal or telephone interview, the Examiner is kindly requested to contact the undersigned at the telephone number listed below.

The USPTO is directed and authorized to charge all required fees, except for the Issue Fee and the Publication Fee, to Deposit Account No. 19-4880. Please also credit any overpayments to said Deposit Account.

Respectfully submitted,



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